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## ECONOMIC EVALUATION

## A Comparison of Different Approaches for Costing Medication Use in an Economic Evaluation

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## ABSTRACT

**Background:** Estimating individual-level medication costs in an economic evaluation can involve extensive data collection and handling. Implications of detailed versus general approaches are unclear. **Objectives:** To compare costing approaches in a trial-based economic evaluation. **Methods:** We applied four costing approaches to prescribed medication data from the Tumour necrosis factor inhibitors Against Combination Intensive Therapy randomized controlled trial. A detailed micro-costing approach was used as a base case, against which other approaches were compared: costing medications used by at least 1.5% of patients; costing medications on the basis of only chemical name; applying a generic prescription charge rather than a medication-specific cost. We quantitatively examined resulting estimates of prescribed medication and total care costs, and qualitatively examined trial conclusions. **Results:** Medication costs made up 6% of the total health and social care costs. There was good agreement in prescribed medication costs (concordance correlation coefficient [CCC] 0.815, 0.819, and 0.989) and excellent agreement in total costs

(CCC 0.990, 0.995, and 0.995) between approaches 1 and 2. Approaches 3 and 4 had poor agreement with approach 1 on prescribed medication costs (CCC 0.246–0.700 and 0.033–0.333, respectively), but agreement on total care costs remained good (CCC 0.778–0.993 and 0.729–0.986, respectively). **Conclusions:** Because medication costs comprised only a small proportion of total costs, the less resource-intensive approaches had substantial impacts on medication cost estimates, but had little impact on total care costs and did not significantly impact the trial's cost-effectiveness conclusions. There is room for research efficiencies without detriment to an evaluation in which medication costs are likely to form a small proportion of total costs.

**Keywords:** costs, economic, medication, trial.

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## Introduction

Central to conducting an economic evaluation is the identification, measurement, valuation, and comparison of the costs and consequences of the alternatives being considered [1]. Once resources have been identified and measured, valuation needs to be completed to provide a cost. Deciding on which costing approach to adopt in an economic evaluation is just as important as deciding what costs to include [1]. The aim of the study, type of patient group, disorder under investigation, treatment comparison, setting, and many more factors will contribute to decisions on how to approach unit costing. Costing medications in economic evaluations can take a considerable amount of time and effort [1]. Individual-level micro-costing (using all detailed information on the resources used) is the most accurate method with more macro-costing

approaches (using general or aggregate valuations) becoming progressively less accurate. The National Institute for Health and Care Excellence (NICE) guide to the methods of technology appraisal 2013 [2] provides methodological recommendations for economic evaluations and recommends that costs should be based on the drug tariffs for medications that are predominantly prescribed in primary care. The International Society for Pharmacoeconomics and Outcomes Research guidelines state that “[d]rug cost values and measurements should be transparent and made available to any reader or user of a CEA,” but do not recommend how costs should be applied to resource use data [3]. There is variation in approaches taken across economic evaluations, with consequent variations in research effort and resourcing. The value of detailed micro-costing, and consequences of less accurate approaches, for an evaluation is unclear.

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Medication is an important factor in the context of overall care and care costs. For many health conditions, medications constitute a small fraction of the total health care cost. For example, the cost of medication in the treatment of schizophrenia has been estimated to account for 2% of direct costs [4]; in multiple sclerosis this is estimated as 8.1% of total costs [5], 13% in lower back pain [6], and less than one-quarter in inflammatory bowel disease [7]. For coronary heart disease, the leading single cause of death in the United Kingdom, the cost of medication has been estimated at only 32% of total health care costs [8].

In these circumstances, when medications represent a very small to moderate proportion of the total direct costs, it is easy to see why a more macro approach to medication costing might be taken, because the impact of imprecision will be minimal in the context of total costs. Nevertheless, when medication is the mainstay of treatment, for example, in chronic conditions without cure (e.g., in moderate to severe chronic psoriasis vulgaris in which medications make up 60% of direct costs [9]), or when medications are particularly expensive, they become a major cost driver in the context of total costs. There are also complications when valuing medications as compared with other types of resources in an economic evaluation because of issues around value and cost [10], but that is beyond the scope of this study.

Using data from a completed within-trial economic evaluation involving participants with rheumatoid arthritis [11,12]—care of which is heavily reliant on management by medication and associated with cost pressures arising from newer, more expensive medications—we applied a number of alternative approaches to costing medication. We then examined the impact of this on 1) total medication costs, 2) total health and social care costs, and 3) the conclusions of the trial.

## Methods

### Data Sources

We used data from the TACIT trial [11,12]. In brief, the Tumour necrosis factor inhibitors Against Combination Intensive Therapy (TACIT) trial was an open-label, multicenter, randomized controlled trial conducted over 12 months in the United Kingdom. Twenty-four clinics recruited patients with active rheumatoid arthritis who met UK criteria for accepting tumor necrosis factor inhibitors (TNFis). Patients were randomized to a treatment strategy of starting either TNFis or conventional disease-modifying antirheumatic drugs (cDMARDs). At 6 months, participants who had not responded adequately to the medication were switched either to another TNFi or, in the case of participants allocated to the cDMARDs arm, to their first TNFi.

The trial included a concurrent economic evaluation. It measured costs from health and social care as well as societal perspectives and linked them with Health Assessment Questionnaire (HAQ) scores and quality-adjusted life-years (QALYs) (on the basis of both the short form 36 health survey [SF-36] and the three-level EuroQol five-dimensional questionnaire [EQ-5D-3L]) at both 6 and 12 months. All resource use was collected using an adapted version of the Client Service Receipt Inventory (CSRI; collected at baseline, 6 months, and 12 months) retrospectively for 3-month periods and extrapolated up to 6-month periods, except trial medications. The CSRI included health and social care costs: inpatient services, outpatient services, primary care services, other community-based services, social services, and other prescribed nontrial medications. Trial medications were recorded separately and prospectively by clinical and research staff over the entire study period using a specifically designed proforma. Details of medication resource use included medication name, dose, frequency, and duration of use. For estimating

costs associated with medications, only generic medication names were taken into account to ensure cost estimations were conservative. All costs are reported in pounds sterling at 2010/2011 prices. Discounting was not necessary because all costs were related to a 1-year period.

In the further analyses reported here, we examine findings only in relation to the health and social care perspectives because the influence of medication costs on total costs would likely be more visible than when applying to more comprehensive perspectives. In addition, this is the perspective currently preferred by NICE in its decision making [2].

In this trial there were two sets of medication data collected: the medication given as part of the trial designated by intervention/control status and all other medications taken for reasons not linked to the trial. It is recommended that the intervention in an economic evaluation be always micro-costed [13]; therefore, we micro-costed the intervention medications as was done in the trial. This is included along with other components in the total health and social care costs. In the comparison of costing approaches, we focused solely on other medications that were prescribed independently from the trial. Because the trial medications were limited to a handful, these were less resource-intensive to value and cost compared with other prescribed medications. In the comparisons, all other cost components were held constant and only the nontrial prescribed medication costing approaches were varied as described herein.

### Costing Approaches

The following four costing approaches were selected for comparison. These are summarized in Table 1.

#### Approach 1: Cost per milligram (base-case analysis)

This criterion standard micro-costing approach [1] was used for the economic evaluation in the TACIT trial [11,12]. A unit cost for each medication was calculated in the form of a cost per milligram. This was calculated on the basis of the most cost-efficient pack size, choosing maintenance prices over initial treatment prices and generic prices over branded ones to obtain conservative estimates. These were based on the recommended dose provided by the British National Formulary [14], which is a reference book that contains information and prices of medication available on the National Health Service. These unit costs were then applied to the data by multiplying the cost per milligram by the dose reported, the number of doses per day, and the number of days used. A series of rules were applied to address missing data in a standardized way. When medication name was missing but other information (e.g., dose) indicated some use, a standard charge based on the prescription cost analysis (PCA) was applied [15]. When a medication name was provided but unit quantity was missing, a cost based on the lowest cost chemical name for that medication from the PCA [15] (or based on the lowest cost individual preparation when chemical name was not available) was applied. When the number of days of use was missing, a PCA cost was used, and the patient was assumed to have received the item once in that period. If patients reported that the frequency of use was “as necessary,” it was assumed that the patient received one prescription during the time period.

#### Approach 2: 1.5% of medications

The second approach used the same micro-costing approach as approach 1 but with an emphasis on the more commonly used medications across the sample. This approach was used by McCrone et al. [16] as a practical approach, given that the service users for their study recorded approximately 1000 medication names. Only those medications that were used by at least 1.5% of

**Table 1 – Details of the four costing approaches.**

Costing method	Prescribed medication	Missing data protocol
<p>Approach 1 (Cost per milligram) This was used as the base-case analysis, which other approaches will be compared against</p>	<ul style="list-style-type: none"> <li>• Cost calculated per milligram on the basis of most efficient pack size</li> <li>• Maintenance prices chosen</li> <li>• Generic prices chosen</li> <li>• On the basis of recommended dose from BNF (If recommended dose given for rheumatoid arthritis, choose this over other recommended doses)</li> <li>• Cost per milligram <math>\times</math> dose <math>\times</math> doses taken per day <math>\times</math> number of days taken in period</li> <li>• Use route/preparation stated by patient</li> <li>• For all creams/ointments, assume one tube lasts a month and use the smallest tube</li> <li>• For dual medications, with milligram and microgram combo drugs, count only the milligrams. If combo of milligram and milligram, add them together</li> </ul>	<p><i>Partial data missing:</i></p> <ul style="list-style-type: none"> <li>• If medication name is missing but other information available, standard charge based on PCA is used.</li> <li>• If unit quantity is missing but medication name is available, cost based on the lowest cost chemical name for that medication from PCA is used, or cost based on PCA charge is used when chemical name is unavailable.</li> <li>• If medication dose is missing, apply the PCA average cost for that drug, assuming each prescription lasts 1 mo or use overall charge if specific medication is not available.</li> <li>• If no route/preparation is given by patient, use what seems most appropriate on the basis of dose, but prioritize tablets and capsules.</li> <li>• If the number of days of medication use is missing, use a PCA item cost and assume that the patient got the item once in that period.</li> <li>• If frequency is “as necessary,” number of days of medication use in each period is missing, use a PCA cost for that drug and assume that the patient got one prescription in each time point.</li> </ul>
<p>Approach 2 (1.5% of medications)</p>	<ul style="list-style-type: none"> <li>• Only medications used by &gt;1.5% of micro-costed</li> <li>• Cost calculated per milligram on the basis of most efficient pack size</li> <li>• Maintenance prices chosen</li> <li>• Generic prices chosen</li> <li>• On the basis of recommended dose from the BNF</li> <li>• Cost per milligram <math>\times</math> dose <math>\times</math> doses taken per day <math>\times</math> number of days taken in period</li> </ul>	<p>As in approach 1.</p>
<p>Approach 3 (Costing according to chemical name)</p>	<ul style="list-style-type: none"> <li>• Cost is calculated according to PCA charge per item on the basis of chemical name as recorded in the BNF</li> <li>• When there are different costs attached to the chemical names, a weighted average will be taken</li> <li>• Assume any PCA charge is 1 month's worth of medication</li> </ul>	<p><i>Partial data missing:</i></p> <ul style="list-style-type: none"> <li>• If medication brand is needed but not specified and there are multiple chemical name options in the PCA, a weighted average will be taken.</li> <li>• If medication name is missing but other information is available, use standard PCA charge.</li> <li>• If unit quantity is missing but medication name is available, cost based on the lowest cost chemical name for that medication from PCA is used, or cost based on PCA charge is used when chemical name is unavailable.</li> <li>• If the number of days of medication use is missing, assume that the patient got the item once in that time period.</li> <li>• If frequency is “as necessary,” the number of days of medication use in each period is missing, assume that the patient got one prescription in each time point.</li> </ul>
<p>Approach 4 (Prescription charge analysis)</p>	<ul style="list-style-type: none"> <li>• Cost calculated by applying standard charge per item on the basis of PCA</li> <li>• Assume any PCA charge is 1 month's worth of medication</li> </ul>	<p><i>Partial data missing:</i></p> <ul style="list-style-type: none"> <li>• If the number of days of medication use is missing, assume that the patient got the item once in that time period.</li> <li>• If frequency is “as necessary,” the number of days of medication use in each period is missing, assume that the patient got one prescription in each time point.</li> </ul>

BNF, British National Formulary; PCA, prescription cost analysis.

**Table 2 – Mean and comparison of prescribed medication costs at each time point for each of the costing approaches.**

Time point	Prescribed medication cost (£), mean $\pm$ SD		Mean difference	95% confidence interval for difference	Paired sample t test	Correlation concordance coefficient	95% limits of agreement
	<b>Approach 1</b>	<b>Approach 2</b>					
Baseline (n = 205)	172 $\pm$ 211	144 $\pm$ 167	28	12 to 43	3.521, $P < 0.001$	0.815	–249, 194
6 months (n = 191)	95 $\pm$ 226	63 $\pm$ 176	33	16 to 49	3.962, $P < 0.001$	0.819	–264, 199
12 months (n = 188)	236 $\pm$ 898	200 $\pm$ 891	35	18 to 53	3.907, $P < 0.001$	0.989	–290, 219
	<b>Approach 1</b>	<b>Approach 3</b>					
Baseline (n = 205)	172 $\pm$ 211	132 $\pm$ 120	40	17 to 63	3.453, $P < 0.001$	0.520	–365, 285
6 months (n = 191)	95 $\pm$ 226	89 $\pm$ 158	7	–14 to 28	0.647, $P = 0.518$	0.700	–303, 290
12 months (n = 188)	236 $\pm$ 898	127 $\pm$ 265	108	–3 to 220	1.913, $P = 0.057$	0.246	–1699, 1482
	<b>Approach 1</b>	<b>Approach 4</b>					
Baseline (n = 205)	172 $\pm$ 211	133 $\pm$ 85	39	13 to 64	3.0122, $P = 0.003$	0.333	–400, 322
6 months (n = 191)	95 $\pm$ 226	99 $\pm$ 85	–3	–32 to 25	–0.234, $P = 0.815$	0.258	405, 412
12 months (n = 188)	236 $\pm$ 898	101 $\pm$ 85	135	13 to 257	2.179, $P = 0.031$	0.033	–1873, 1603

\*Covers a 3-mo period.

the sample were costed and included. For obvious reasons, medication resource use with missing medication names could not be included in this approach. Unit cost calculations and approaches to missing data were the same as in approach 1.

### Approach 3: Chemical name

The third approach is one used by Powell et al. [17]. This involves costing all medications but calculating unit costs differently. Unit costs were calculated for each medication by looking up the cost of a prescription for that medication's chemical name according to the PCA. An arbitrary assumption was made that one PCA prescription charge represents 1 month's worth of medication. The number of PCA charges assigned to each medication was based on the number of days of use reported by the patient. For example, if a patient took a medication for up to and including 30 days, we took this to indicate one prescription and therefore one prescription charge. Accordingly, we assumed that 31 to 60 days of use indicated two prescriptions and 61 to 90 days of use indicated three prescriptions. The number of prescription charges was then multiplied by the chemical name net ingredient cost of the medication. When a medication brand was not specified and multiple chemical names were offered in the PCA, an overall average PCA charge was applied. When medication names were missing but other information was available, for example, number of days of medication use, a standard PCA charge was used. If the unit was missing but the medication name was given, the cost was generated on the basis of the lowest cost chemical name for the medication provided from the PCA. When the number of days of medication use was missing, an assumption was made that the patient received the item once during the time period. When frequencies were reported as "as necessary," an

assumption was made that the patient received one prescription during the time period.

### Approach 4: Prescription charge analysis

The final approach is the most macro approach, which was used in the valuation of some medications by Amiel et al. [18]. The unit cost of each medication was taken as an overall total PCA charge per item. This is the net ingredient cost average for all medications listed in the PCA (£9.16). As with approach 3, the PCA charge was multiplied by the number of days of medication use (0–30 days assumed to be one prescription, 31–60 days indicating two prescriptions, and 61–90 days indicating three prescriptions) to give the medication costs, and missing medication name or days on medication were dealt with as in approach 3.

### Analysis

Data were analyzed using STATA 11 (StataCorp LP, College Station, TX). Taking the base-case approach as a comparator, we compared each approach's respective impacts on estimates of total medication costs, estimates of total health and social care costs, and the resulting cost-effectiveness conclusions of the study.

The total mean cost of prescribed medications produced by each approach was compared using paired sample t tests (confirmed by Wilcoxon rank sum tests to account for non-normal distribution). Overall agreement was measured using the Lin concordance correlation coefficient (CCC) and limits of agreement [19], which has been shown to be a more appropriate measure than the Pearson correlation [17,19,20]. A CCC of 1 indicates perfect agreement and of –1 indicates perfect inverse agreement.

According to Cicchetti [21], less than 70% agreement is poor, 70% to 79% is fair, 80% to 89% is good, and 90% to 100% is excellent.

Total health and social care costs produced by each costing approach are also compared using paired sample *t* tests and CCCs. Incremental cost-effectiveness ratios (ICERs)/incremental cost-utility ratios were calculated on the basis of the resultant health and social care costs from each approach. Because the resource use data were recorded for a 3-month (rather than a 6-month) period at each follow-up point, the associated cost data were multiplied by 2 to extrapolate to a full 12-month period as per the approach used in the TACIT trial base-case economic evaluation. Cost-effectiveness acceptability curves (CEACs) based on the net-benefits approach were also created to explore uncertainty. Estimates of mean costs and outcomes used to calculate ICERs included covariates for baseline HAQ score, duration of illness, age, sex, region, ethnicity, and baseline costs/outcome as appropriate.

## Results

### Sample

The results reported are based on the 205 patients recruited and randomized in the trial of which 152 (74%) were female, 181 (88%) were of white ethnic origin, and mean age was  $57 \pm 11.97$  years. The mean duration of illness was  $8 \pm 8.82$  years. Of the 205 patients, all (100%) had CSRI data (and therefore prescribed medication data) available at baseline, 191 (93%) at 6 months, and 188 (92%) at 12 months. Only these patients with prescribed medication and

health and social care use data were included in the comparisons of costs. Some of these participants, however, had missing outcomes data and so were not included in subsequent comparisons of cost-effectiveness estimations. The lowest number of participants included in any cost-effectiveness analysis, because they had both cost and outcome data, was 186 out of 205 (91%).

### Impact on Prescribed Medication Cost Estimates

The mean costs of the prescribed medications at each time point for each of the costing approaches are presented in Table 2. We have presented the mean costs of the prescribed medications for the intervention and control arms combined, because the focus is to compare costing approaches (see Scott et al. [12] for economic evaluation trial results). It appears that the medication costs drop dramatically between baseline and 6-month follow-up. This is because medication at baseline is included in the prescribed medication category, whereas at 6 months, medication is divided into prescribed medication and trial medication. The mean cost of prescribed medication at baseline was  $\pounds 172 \pm \pounds 211$  on the basis of approach 1 compared with  $\pounds 144 \pm \pounds 167$ ,  $\pounds 132 \pm \pounds 120$ , and  $\pounds 133 \pm \pounds 85$  on the basis of approaches 2, 3, and 4, respectively. This was lower at 6 months with a mean cost of prescribed medication of  $\pounds 95 \pm \pounds 226$  on the basis of approach 1 compared with  $\pounds 63 \pm \pounds 176$ ,  $\pounds 89 \pm \pounds 158$ , and  $\pounds 99 \pm \pounds 85$  on the basis of approaches 2, 3, and 4, respectively. At 12 months, these were  $\pounds 236 \pm \pounds 898$ ,  $\pounds 200 \pm \pounds 891$ ,  $\pounds 127 \pm \pounds 265$ , and  $\pounds 101 \pm \pounds 85$  on the basis of approaches 1, 2, 3, and 4, respectively.

Results indicate that although there is a statistically significant difference in prescribed medication costs produced by

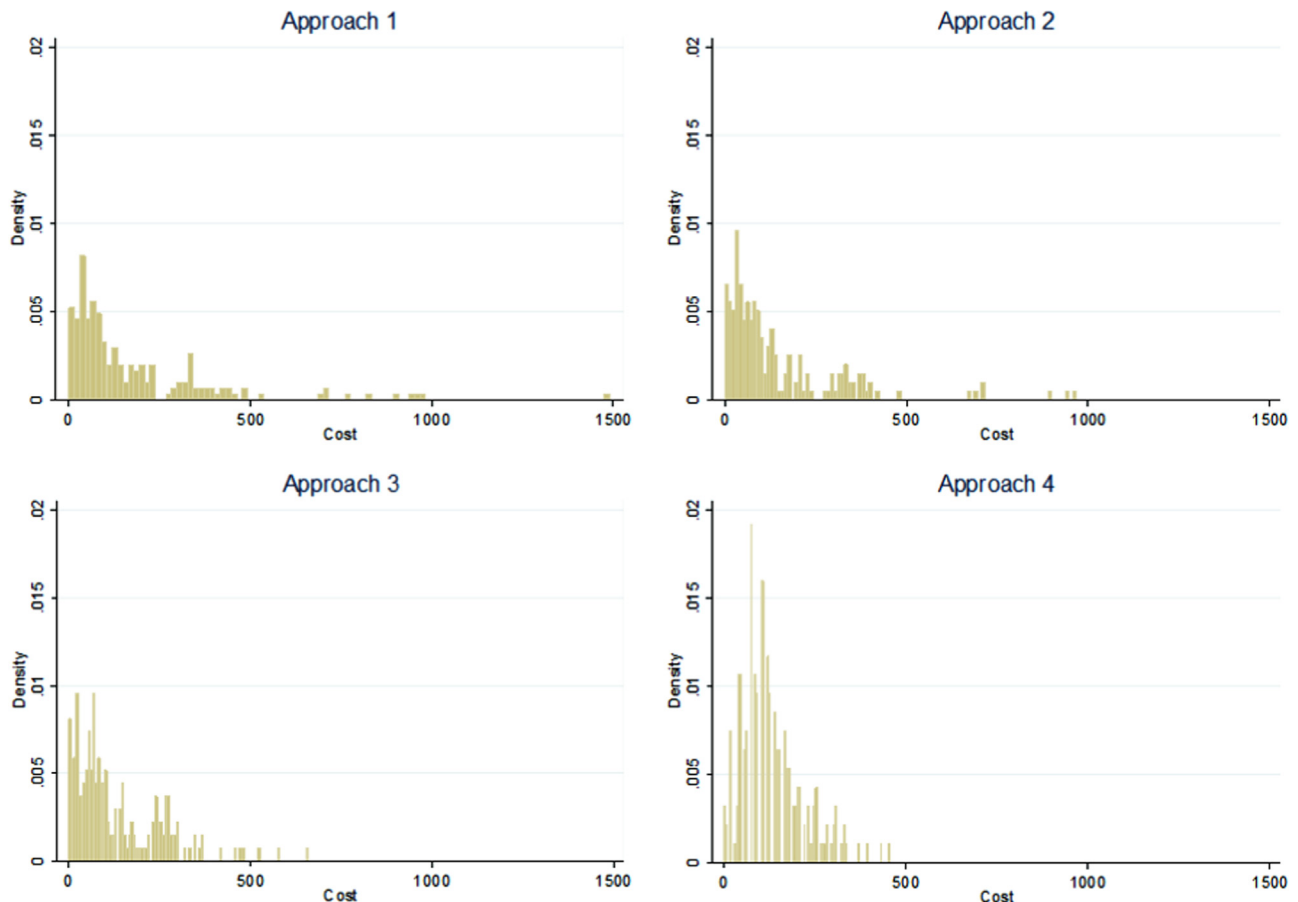


Fig. 1 – Histograms showing the distribution of medication costs using each costing approach (baseline).



**Table 3 – Mean and comparison of health and social care costs at each time point for each of the costing approaches (including all medications).**

Time point	Health and social care cost (£), mean $\pm$ SD		Mean difference	95% confidence interval for difference	Paired sample t test	Correlation concordance coefficient	95% limits of agreement
	<b>Approach 1</b>	<b>Approach 2</b>					
Baseline (n = 205)	1335 $\pm$ 1665	1279 $\pm$ 1639	56	24 to 87	3.521, $P < 0.001$	0.990	–499, 388
6 months (n = 191)	3417 $\pm$ 2570	3348 $\pm$ 2542	69	35 to 104	3.925, $P < 0.001$	0.995	–548, 410
12 months (n = 188)	3781 $\pm$ 2798	3705 $\pm$ 2788	76	37 to 115	3.829, $P < 0.001$	0.995	–606, 455
	<b>Approach 1</b>	<b>Approach 3</b>					
Baseline (n = 205)	1335 $\pm$ 1665	1255 $\pm$ 1644	80	34 to 125	3.453, $P < 0.001$	0.979	–729, 569
6 months (n = 191)	3417 $\pm$ 2570	3403 $\pm$ 2623	14	–31 to 59	0.615, $P = 0.539$	0.993	–628, 600
12 months (n = 188)	3781 $\pm$ 2798	3544 $\pm$ 2300	236	–7 to 480	1.914, $P = 0.057$	0.778	–3556, 3083
	<b>Approach 1</b>	<b>Approach 4</b>					
Baseline (n = 205)	1335 $\pm$ 1665	1257 $\pm$ 1645	78	27 to 128	3.0122, $P = 0.003$	0.974	–800, 645
6 months (n = 191)	3417 $\pm$ 2570	3423 $\pm$ 2573	–6	–67 to 56	–0.185, $P = 0.854$	0.986	–841, 852
12 months (n = 188)	3781 $\pm$ 2798	3484 $\pm$ 2247	297	31 to 563	2.202, $P = 0.029$	0.729	–3923, 3329

\* Health and social care costs include nonmedication costs, prescribed medication, and trial medications. Costs are extrapolated up to 6-month periods (except trial medications that covered 6 mo).

approaches 1 and 2 at baseline, 6 months, and 12 months ( $t = 3.521$ ,  $P < 0.001$ ;  $t = 3.962$ ,  $P < 0.001$ ;  $t = 3.907$ ,  $P < 0.001$ , respectively), there is still a good to excellent level of agreement (CCC 0.815, 0.819, and 0.989, respectively). In contrast, the comparison of approach 1 with approaches 3 and 4 shows poor agreement at baseline, 6 months, and 12 months (CCC 0.520, 0.700, and 0.246, respectively, for approach 3 and CCC 0.333, 0.258, and 0.033, respectively, for approach 4). In Figure 1, we have presented four overlapping histograms in addition to show the distribution of medication costs for each costing approach. The distribution shows that as we move from approach 1 to approaches 2, 3, and 4, the few cases with larger costs become less and the frequency of the lower costs increases. This is for baseline data, but similar patterns were found for 6-month and 12-month data also.

### Impact on Health and Social Care Cost Estimates

The mean health and social care costs at each time point for each of the costing approaches are presented in Table 3. For each approach, the prescribed medications made up the following proportions of the total health and social care costs at baseline, 6 months, and 12 months: 11% to 13%, 2% to 3%, and 3% to 6%, respectively.

At 6 months, mean health and social care costs were £3417  $\pm$  £2570 on the basis of approach 1 compared with £3348  $\pm$  £2542, £3403  $\pm$  £2623, and £3423  $\pm$  £2573 on the basis of approaches 2, 3, and 4, respectively. At 12 months, these were £3781  $\pm$  £2798, £3705  $\pm$  £2788, £3544  $\pm$  £2300, and £3484  $\pm$  £2247 on the basis of approaches 1, 2, 3, and 4, respectively.

There was little variation across all approaches within each time point. The mean difference between approaches 1 and 2 is very

small for all three time points and again results indicate that although there is a statistically significant difference in prescribed medication costs produced by approaches 1 and 2 at baseline, 6 months, and 12 months ( $t = 3.521$ ,  $P < 0.001$ ;  $t = 3.925$ ,  $P < 0.001$ ;  $t = 3.829$ ,  $P < 0.001$ , respectively), there is still an excellent level of agreement (CCC 0.990, 0.995, and 0.995, respectively).

The comparison of approaches 1 and 3 and approaches 1 and 4 shows excellent agreement at baseline and 6 months (CCC 0.979 and 0.993, respectively, for approach 3 and CCC 0.974 and 0.986, respectively, for approach 4), whereas the 12-month comparison shows a poor level of concordance (CCC 0.778 for approach 3 and CCC 0.729 for approach 4).

### Impact on ICER Estimates

ICERs based on the HAQ at 6 months suggest an ICER between £51,643 and £53,363, with approach 1 and approach 4 producing the lowest and the highest estimates, respectively (Table 4). ICERs based on the HAQ at 12 months ranged between –£11,780 and –£12,605, with approach 3 and approach 2 producing the lowest and the highest estimates, respectively. All ICERs based on QALYs suggest that cDMARDS are more likely to be cost-effective compared with TNFis (according to NICE's recommendation of £20,000–£30,000 per QALY). ICERs based on 6-month data (from either the EQ-5D-3L or the SF-36) ranged from –£3,615 to –£3,735, with approach 1 and approach 4 producing the lowest and the highest QALYs, respectively. On the basis of 12-month data, approach 3 and approach 2 produced the lowest and the highest ICERs, with the SF-36-derived ICERs ranging from –£188,480 to –£201,672 and the EQ-5D-3L-derived ICERs ranging from –£94,240 to –£100,836.

**Table 4 – Cost-effectiveness and cost-utility summaries at 6 mo and 12 mo on the basis of each of the four approaches.**

Time point/approach	Cost per additional point on the HAQ (£)	Cost per additional QALY (SF-36–based) (£)	Cost per additional QALY (EQ-5D-3L–based) (£)
6 months			
Approach 1	51,643	–3615	–3615
Approach 2	52,509	–3676	–3676
Approach 3	53,238	–3727	–3727
Approach 4	53,363	–3735	–3735
12 months			
Approach 1	–12,063	–193,000	–96,500
Approach 2	–12,605	–201,672	–100,836
Approach 3	–11,780	–188,480	–94,240
Approach 4	–12,037	–192,587	–96,293

EQ-5D-3L, three-level EuroQol five-dimensional questionnaire; HAQ, Health Assessment Questionnaire; QALY, quality-adjusted life-year; SF-36, short form 36 health survey.

### Impact on Probability of Cost-Effectiveness Estimates

CEACs based on QALYs (derived from either the EQ-5D-3L or the SF36) showed that the probability that the cDMARDs group is cost-effective compared with the TNFis group from a health and social care perspective is 99% or higher at all willingness-to-pay thresholds on the basis of all four costing approaches. Equivalent probabilities based on the HAQ were 100% for thresholds of up to £10,000 per point improvement on the HAQ but decreased at higher willingness-to-pay thresholds, to around 45% at a threshold of £50,000. This was true for all four costing approaches.

At 12 months, all CEACs based on all approaches suggested that cDMARDs have a 99% or higher probability of being cost-effective compared with TNFis at all willingness-to-pay values of up to £50,000.

## Discussion

Because the medication costs comprised only a small proportion (6%) of total costs, the less resource-intensive approaches had substantial impacts on estimates of medication costs, but had little impact on total care costs and thus did not significantly impact on the trial's cost-effectiveness conclusions.

There was good agreement in prescribed medication costs between the cost per milligram approach (approach 1) and the 1.5% of medications approach (approach 2) but not between the chemical name approach (approach 3) and the prescription charge analysis approach (approach 4) compared with the cost per milligram approach (approach 1). On this basis one might conclude that the 1.5% of medications approach is the only approach that could be reliably used in lieu of the criterion standard cost per milligram approach. Nevertheless, with the 1.5% of medications approach, there is a risk of excluding high-cost medications used by a few participants that may in total amount to more expense than low-cost medications used by many. Agreement on health and social care costs remained good to excellent between approach 1 and all other approaches. Hence, the impact of differences in prescribed medication costs on health and social care costs was low. This is because prescribed medication costs were a small proportion of the overall health and social care cost (~6%). Subsequently, there were inconsequential impacts of the different costing approaches on the ICERs, CEACs, and the conclusions of the study.

The results support the argument that if medication costs were a large proportion of the overall cost, then approaches 3 and

4 may not be appropriate. Furthermore, in approaches 3 and 4, detail is lost on the more expensive drugs used by patients. A drug that has a cost of over £1000 becomes less than £10 when using approach 4. Therefore, in studies that include high-cost medications, gross underestimation can occur.

It is notable that although high correlations are reported for most approaches, the paired sample *t* tests indicated that the approaches are significantly different (in most cases). The CCC and *t* test results have different meanings, and hence they do not necessarily support one another. The CCC indicates that the cost values are moving in the same overall direction; it shows whether the approaches have positive values or negative values. Here there is an acceptance that the measures are not expected to be exactly the same, but it deciphers whether the effects are parallel to one another and whether the change is alike. The paired *t* test looks for the values to be exactly the same, and therefore it will confirm that the approaches are significantly different because the values cannot be exactly the same given the different methodology. Therefore, the results from the *t* tests do not undermine the results from the CCC but indicate some level of difference between comparisons.

No other research has compared different approaches for costing medication. Nevertheless, previous research comparing two methods of collecting resource use data in primary care (general practitioners' case records and a self-complete postal questionnaire) has reported a CCC of 0.756 as good and concludes that either can be used without undermining the data quality [22]. With all CCCs between the cost per milligram approach and the 1.5% of medications approach being more than 0.9, this consistency is even higher.

The problem of missing data is frequent in cost-effectiveness analyses [23,24] because of issues with medication misspelling and/or phonetic pronunciation, poor recall around medication name, dose start and end dates, and frequent dose changes. Medication costing and approaches to handling missing medication data are intertwined as demonstrated here, and Faria et al. [23] have suggested appropriate ways to deal with such missing data. Nevertheless, perhaps the key to dealing with these issues is to mitigate for these problems earlier in the research process in terms of greater attention to what data are collected and how. Prospectively completed patient diaries and administrative databases are alternatives that may provide fuller data compared with retrospective self-reports of medication use. There are, however, trade-offs to be made. For example, diaries may potentially be more reliable for those who complete them but they still carry a risk of complete nonresponse, and



administrative databases may have increased completeness and reliability may carry greater research burdens (e.g., people with psychosis could be prescribed/provided with medication from hospital pharmacies, community mental health teams, or general practitioners, all of whom have separate databases with different mechanisms for medication recording). Nevertheless, our study suggests that if medication costs are likely to be a small proportion of total costs, a detailed costing approach may not be needed, which would reduce the amount of data needed. This could allow patients to report much less and simpler details about their medication usage.

This is a single study based on one trial and economic evaluation in one disease area. Further research on the impact of costing medications should be undertaken, particularly in diseases for which prescribed medication plays a large part in overall costs. Furthermore, medication data in this study were collected using the nongeneric name of drugs. This could have led to underestimates in drug costs from approaches 1 and 2, which may have driven costs in these approaches down, compounding differences in findings between approach 1 and approaches 3 and 4. In addition, participants lost to follow-up may have had medication use that was different from those who were followed-up and may have skewed results. This needs to be explored in further studies.

This study has indicated that a range of alternative and possibly more efficient costing approaches for medications, other than micro-costing, are able to generate the same conclusions for cost-effectiveness and cost-utility analyses. This is likely dependent on the level of contribution that medications make to overall care and care costs. The conclusions for the TACIT economic evaluation remain unchanged when different prescribed medication and health and social care costs are substituted. Although researchers should carefully consider appropriate costing approaches in each situation, there is scope for research efficiencies when medication costs are likely to be overshadowed by other care costs.

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